

## REMARKS/ARGUMENTS

After entry of this paper, claims 4-18, 22, 25, 30, and 32-39 are pending. Claims 25, 30, and 33 are amended to clarify the invention and are supported in the originally filed specification and claims, specifically at page 14, lines 21-22, page 20, lines 19-21, and page 82, Table 1.

These claims are also amended to require that the antisense compounds of the invention are non-cleaving. This non-cleaving embodiment of the invention is inherently supported in the specification and particularly in the description of preferred oligonucleotides at page 14, line 28 through page 15, line 16; page 23, lines 28-31; page 28, line 21 through page 29, line 9; and page 82, Table 1. None of the oligonucleotides which hybridize directly to the target sequence of apo(a) SEQ ID NO: 4 have cleaving ability. None of the oligonucleotides exemplified in Table 1 have any catalytic or cleaving regions and thus are examples of non-cleaving oligonucleotides of this invention. Further, it is inconsistent with the function of a primer as suggested in on pages 28-29 for a oligonucleotide to have a cleaving function. Further, the only "cleaving" function ever mentioned in the specification is when the oligonucleotide is a specific type of chimeric compound described on page 41, line 27 through page 42, line 8. By contrast the other chimeric compounds described at page 42, lines 9-14 and exemplified in the Examples have no cleaving function. Thus, the

specification is believed to clearly support the use of the term "non-cleaving".

New claims 37-39 are added to recite another embodiment of the invention supported in the originally filed specification and claims, and particularly at page 82, Table 1. New claims 37-39 are supported specifically on page 11, 15-18 of this specification, which excludes ribozymes from the class of compounds used in the methods of this invention.

The description of oligonucleotides as non-cleaving or as excluding ribozymes are also supported in the specification and examples of the parent US Patent Application No. 09/923,515, particularly in the description of the oligonucleotides listed in Example 15 and in the distinction made by the inventors in reference to "antisense oligonucleotides" and "other antisense compounds" on page 11, line 26 through page 12, line 4.

As the Examiner is aware, MPEP § 2163 provides that there is "...no *in haec verba* requirement..." for newly added claim subject matter and that the same "...must be supported in the specification through express, implicit, or inherent disclosure" (emphasis added). In view this section and above-noted remarks regarding support in the specification for "non-cleaving", Applicants assert that identification of the antisense compounds of the invention as "non-cleaving" is well supported by the specification and finds more than adequate written description. While Applicants do not believe that it is necessary to amend the specification to specifically recite that the antisense compounds discussed therein are "non-cleaving" (which is

receptive to making such an amendment if so instructed by the Examiner.

The specified sections of the specification were amended to correct clerical errors and to provide sequence listing identifiers for sequences that were present in the originally filed specification.

No new matter is added by these claim and specification amendments and new claims.

### **Specification Objection**

*The Examiner objected to the specification under 37 CFR §§ 1.821-1.825 and asserted that the specification contains three sequences on page 62 that are not identified by SEQ ID NOs.*

Applicants respectfully request reconsideration and withdrawal of this rejection for the following reasons.

In an effort to correct a clerical error, Applicants amended the sequence listing to include the sequence provided on page 62, lines 1-7 of the specification. No new matter is added by this amendment.

In accordance with 37 CFR § 1.825, since these sequences were present in the originally filed application, the inclusion of the same in the enclosed substitute sequence listing does not add new matter.

Further, in accordance with 37 CFR § 1.825(b), Applicants submitted an electronic version of the substitute sequence listing on May 25, 2005. Applicants have enclosed an Acknowledgement Receipt from the USPTO indicating receipt of the electronic version of the sequence listing. This electronic version of the

substitute sequence listing is identical to the paper copy of the substitute sequence listing enclosed herewith.

Reconsideration of this rejection is requested.

#### Information Disclosure Statements

1. *The Examiner asserted that the Information Disclosure Statement filed on January 10, 2005 will be considered once it is available for review.*

Applicants respectfully request that the Examiner consider the documents cited in the IDS filed on January 6, 2005 prior to issuance of a Notice of Allowance.

2. *New Supplemental Information Disclosure Statement*

Applicants respectfully request that the examiner consider the following documents disclosed in the attached supplemental IDS:

- a. the published PCT application corresponding to US Patent Application No.09/923,515, namely International Patent Publication No. WO 03/014307;
- b. the published PCT application corresponding to related US Patent Application No. 10/485,113, namely International Patent Publication No. WO 05/000201;
- c. a new document cited by Examiner Gibbs in US Patent Application No. 09/923,515's Office Action of April 6, 2005 - Prosnyak et al. (Genomics, 21:490-494 (1994) and
- d. a new document cited by Examiner Gibbs in US Patent Application No. 09/923,515's Office Action of April 6, 2005 - Devarre et al. (Nucleic Acids Research 25:3584-3589 (1997)).

Additionally, because parent US Patent Application No. 09/923,515 is being handled by a different examiner, Applicants further supply the examiner with copies of Office Actions in the parent application:

- e. the substantive Office Action, dated March 19, 2003;
- f. the substantive Office Action dated March 9, 2004; and
- g. the substantive Office Action dated April 6, 2005.

**35 USC § 112, First Paragraph Rejection**

*Claims 2-19, 22, 25, 30, and 32-35 are rejected under 35 USC § 112, first paragraph for the following reasons.*

- (i) *The Examiner asserted that although the specification describes antisense sequences (Table 1), there is no specific description provided of a sequence to any other version of species of apolipoprotein (a) that will bind to any other apolipoprotein (a) sequence.*

Applicants respectfully request reconsideration and withdrawal of this rejection for the following reasons.

The cancellation of claims 2-3 moots the outstanding rejection moot as to these claims.

In an effort to place the application in condition for allowance, Applicants amended claims 25, 30 and 33 to specify the apolipoprotein(a) sequence of SEQ ID NO: 4. All remaining claims rejected on this basis are dependent therefrom. As amended, the claims refer to a specific apolipoprotein(a) sequence.

Reconsideration of this rejection is requested.

- (ii) *The Examiner asserted that the although the specification enables inhibition of apolipoprotein (a) expression in vitro, it does not provide reasonable enablement for the inhibition of such cells in vivo or the treatment of an animal as claimed in claims 2-19, 22, 25, 30, and 32-35.*

Applicants respectfully request reconsideration and withdrawal of this rejection for the following reasons.

The cancellation of claims 2-3 moots the outstanding rejection moot as to these claims.

To support the assertion in the specification that the antisense compounds of the present invention inhibit expression of apolipoprotein(a) *in vivo* and are thus useful in treating disorders associated with apolipoprotein(a), Applicants have enclosed a Rule 132 Declaration executed by a co-inventor of this application. In this Declaration, Applicants have provided mouse model data demonstrating that inhibition of murine apolipoprotein(a) can be achieved *in vivo* using an exemplary antisense compound of the invention. These data provide sufficient data to support the disclosure of this specification and the pending claims.

Reconsideration of this rejection is requested.

**35 USC § 112, Second Paragraph Rejection**

*The Examiner rejected claim 19 under 35 USC § 112, second paragraph for being drawn to a non-elected invention.*

The cancellation of non-elected claim 19, without prejudice, moots the outstanding rejection.

**35 USC § 102 Rejection**

*Claims 2, 4, 5, 7, 10-13, 14, 15, 19, 22, and 25 are rejected under 35 USC 102(b) over Morishita et al. (Circulation, 98:1898 (1998)).*

*The Examiner asserted that Morishita teaches three phosphorothioate modified ribozyme oligonucleotides and one DNA oligonucleotide, all 42 bp in length, and targeted to kringle 4 of apolipoprotein(a).*

Applicants respectfully request reconsideration and withdrawal of this rejection for the following reasons.

The cancellation of claim 2 renders the outstanding rejection moot as to this claim.

Applicants' amended claims are directed to methods of using antisense compounds 15 to 30 nucleobases in length that hybridize to and inhibit expression of Apo(a). These claims require that the compounds inhibit the expression of Apo(a), regardless of whether they also inhibit another target, e.g., plasminogen, and that the compounds are non-cleaving. The specification clearly sets out the requirement for the antisense compounds used in the methods to inhibit Apo(a) and provides sufficient written description to permit one to determine whether or not such compounds do so. The specification also provides support for the antisense compounds of the claimed invention to be non-cleaving as evidenced by the selected portions of the specification identified above.

In contrast, Morishita is directed to the use of ribozymes (see, e.g., RZ120, RZ151, RZ164 and mRZ151) and to a DNA oligonucleotide (DNA-RZ151), which ribozymes and sequence are each about 42 nucleobases in length and contain catalytic regions that do not hybridize to the

Morishita specifically distinguishes between the use of "antisense ON that are complementary to the mRNA of interest" and the use of "ribozymes, a unique class of RNA molecules that not only store information but also process catalytic activity." (see page 1899, col. 1, lines 1-3). Morishita also refers to the ribozymes as ribozyme ON (i.e., oligonucleotides), but clearly draws the distinction based on catalytic activity. For example, on page 1900, col. 2, last paragraph, Morishita discusses that the ribozymes "cleave" the apo(a) mRNA. Further, as known by those of skill in the art, even minimal ribozymes require about 40 nucleotides in length to properly operate (including the size of the stem-loop, catalytic region and antisense arms)<sup>1</sup>, which are not encompassed by the presently claimed invention.

Morishita does not teach antisense oligonucleotides that are 15 to 30 nucleobases in length that are **non-cleaving**. In contrast, Morishita in fact teaches away from the present invention by only providing compounds, i.e., ribozymes, that are capable of cleaving. Morishita therefore cannot and does not teach Applicants' invention.

Morishita is an ineffective anticipatory reference for use in this rejection because its compounds fail to meet all structural requirements of the amended claims and in fact teach away from the same.

Reconsideration and withdrawal of this §102(b) rejection is thereby requested.

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<sup>1</sup> See, e.g., T. Ohmichi and E. Kool, 2000 Nucl. Acids Res., 28 (3):776-783

**35 USC § 103 Rejection**

*Claims 2-18, 22, and 25 are rejected under 35 USC 103(a) over Morishita et al., in view of Frank et al. (Gene Therapy, pages 425-430 (2001)) and further in view of Baracchini et al. (US Patent No. 5,801,154).*

*The Examiner asserted that it would have been obvious to make an antisense oligonucleotide to apolipoprotein(a) as taught by Frank to inhibit apolipoprotein(a) as shown by Morishita in combination with the modification and oligonucleotide length taught by Baracchini.*

Applicants respectfully request reconsideration and withdrawal of this rejection for the following reasons.

The cancellation of claims 2-3 renders the outstanding rejection moot as to these claims.

Further, the enclosed 131 Declaration establishes conception of the present invention prior to the cited Frank reference. Therefore, since Frank should properly be removed as a reference, this rejection is rendered moot and should be withdrawn.

**Double Patenting Rejections**

- (i) *Claims 2-19, 22, 25, 30, and 32-35 are rejected under the judicially created doctrine of obviousness-type double patenting over claims 1, 2, 4-11, and 15-20 of US Patent Application No. 10/485,113 ('113).*

Applicants would like to defer addressing this rejection until the claims are otherwise in condition for allowance.

- (ii) *Claims 2-19, 22, 25, and 33 are rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-10 and 15 of US Patent Application No. 09/923,515.*

Applicants would like to defer addressing this rejection until the claims are otherwise in condition for allowance.

In view of the above amendments and remarks, Applicants submit that these amended claims are in condition for allowance and request that the examiner permit same to proceed to issue in due course.

The Director is hereby authorized to charge any deficiency in any fees due with the filing of this paper or during the pendency of this application, or credit any overpayment in any fees to our Deposit Account Number 08-3040.

Respectfully submitted,

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